

Teratogens and drug of abuse in pregnancy

Lecture-2-
Reproductive Block
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Teratogens

- During pregnancy the focus must be to eliminate potentially toxic agents that may harm the mother or unborn child
- Agents that cause fetal malformations are termed **teratogens**
- **Teratos** in Greek means monster



Teratogens

- Uses of **certain types of drugs during pregnancy** could cause **birth defect** and **congenital malformation**, a synonymous terms used to describe structural, behavioural, functional and metabolic disorders present at birth
- **Birth defect** are the leading cause of infant mortality

Teratogens

- Until the early **1940s** it was assumed that congenital defects were caused primarily by **hereditary factors**
- With the discovery by Gregg that German measles affecting a mother during early pregnancy caused abnormalities in the embryo, it suddenly became evident that congenital malformations in human could also be caused by environmental factors
- In **1961** observations by Lenz linked limb defects to the sedative **thalidomide** and made it clear that drugs could also cross the placenta and produce birth defects
- Since that time many agents have been identified as **teratogens**

Teratogens

- **Thalidomide** disaster (1958-61) open the eyes of various nations and they made it mandatory to impose strict **teratogenicity** tests before a new drug is approved for use
- The sedative thalidomide taken during pregnancy for relief from morning sickness, resulted in thousands of babies being born with **phocomelia** (seal limbs)



Examples of Teratogenic agents

Teratogen	Congenital Malformation
Thalidomide	Phocomelia (Limb defect), heart malformations
Phenytoin	<u>Fetal hydantoin syndrome</u> : facial defects, mental retardation
Valproic acid	Neural tube defects, heart, craniofacial and limb anomalies
Lithium	Heart malformations
Live vaccine	Spontaneous abortion, premature births, possible congenital defect
Warfarin	Chondrodysplasia, microcephaly
Statin	Malformations, anal atresia, esophageal atresia

Examples of Teratogenic agents

Teratogen	Congenital Malformation
ACE inhibitors	Growth retardation, fetal death
Isotretinoin (vitamin A)	<u>Vitamin A embryopathy</u> : small, abnormally shaped ears, mandibular hypoplasia, cleft palate, heart defects
Androgenic agent	Masculinisation of female genitalia: fused labia, clitoral hypertrophy
Diethylstilbestrol	Malformation of the uterus, uterine tubes, and upper vagina, vaginal cancer, malformed testes
Antineoplastic	They are embryocidal, fetal anomalies, growth restrictions



Cleft Lip



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Cleft Palate



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Spina Bifida

Anencephaly

Encephalocele

Principles of Teratology

Factors determining the capacity of an agents to produce birth defects include the following:

- ✓ **Genotype of the conceptus** and **maternal genome**
- ✓ **Development stage** at the time if exposure
- ✓ **Dose** and **duration** of exposure to a teratogen
- ✓ **Mechanism of teratogens** initiate abnormal pathogenesis, e.g., cell death, decreased cell proliferation, or inhibition of specific biochemical or molecular process
- ✓ **Manifestation of abnormal development** are death, malformation, growth retardation, and functional disorders

Fetal Growth From 8 to 40 Weeks



- Depending on the stage of pregnancy during which teratogen is administered, it can produce various abnormalities:
 - Conception to 16 days:** usually resistant to teratogenic effects. If affected abortion occurs
 - Period of organogenesis (17 to 55 days of gestation):** Most vulnerable period, all major organ system developed structurally; **major congenital anomalies** occur. **Physical abnormalities and structural defects** such as: cardiac abnormality, spina bifida and limb defect could happen
 - Fetal period (56 days onward):** period of growth development and functional, hence **development and functional defect may occur; minor congenital anomalies**

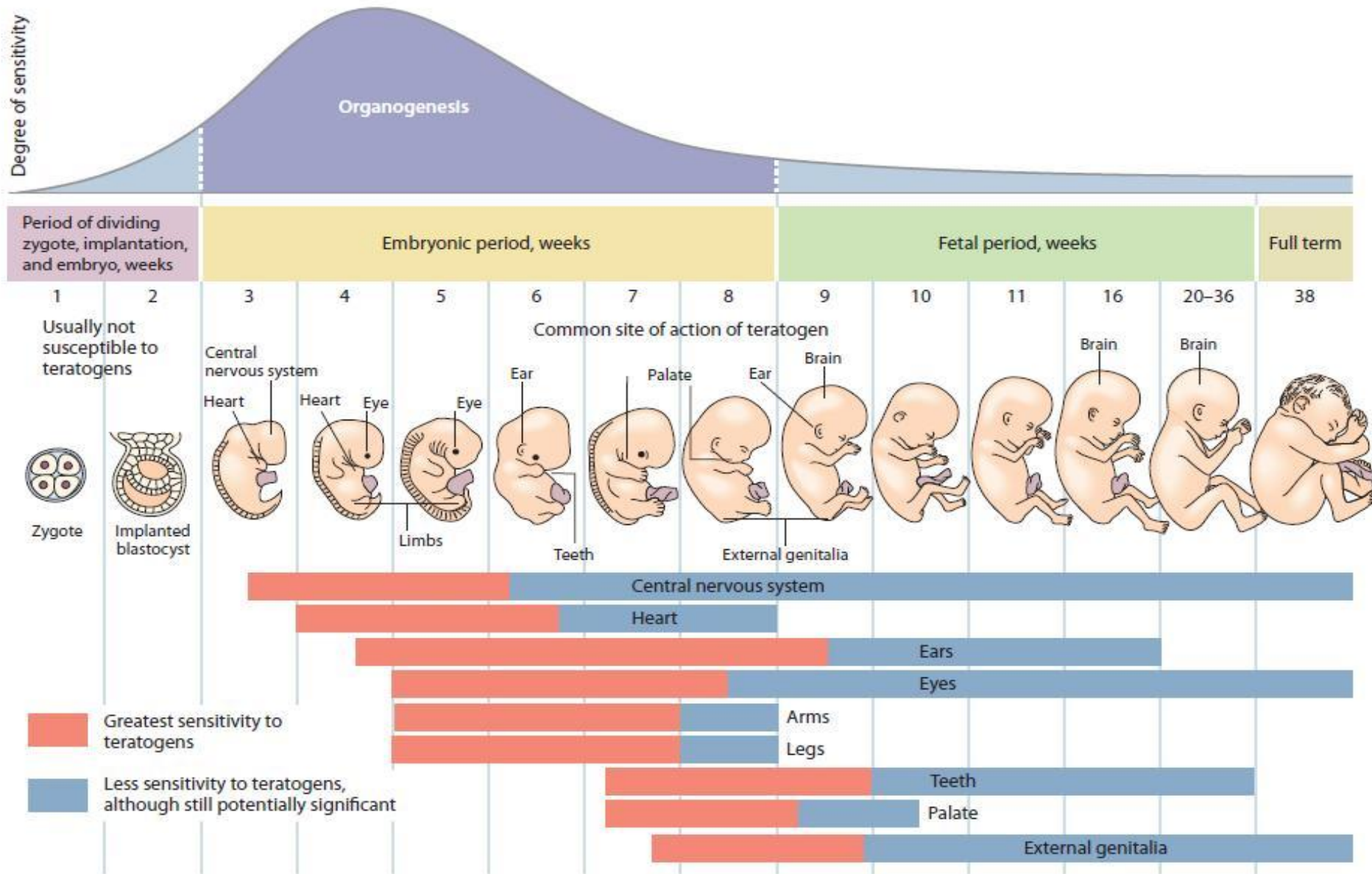


FIGURE 3.5

TERATOGENS AND THE TIMING OF THEIR EFFECTS ON PRENATAL DEVELOPMENT. The danger of structural defects caused by teratogens is greatest early in embryonic development. The period of organogenesis (red color) lasts for about six weeks. Later assaults by teratogens (blue-green color) mainly occur in the fetal period and instead of causing structural damage are more likely to stunt growth or cause problems of organ function.

First trimester of pregnancy

- In general, *drugs should be avoided* during pregnancy especially in the **first trimesters (i.e. 0 to 3 months)**; when the skeleton and major organs begin to develop

9th week

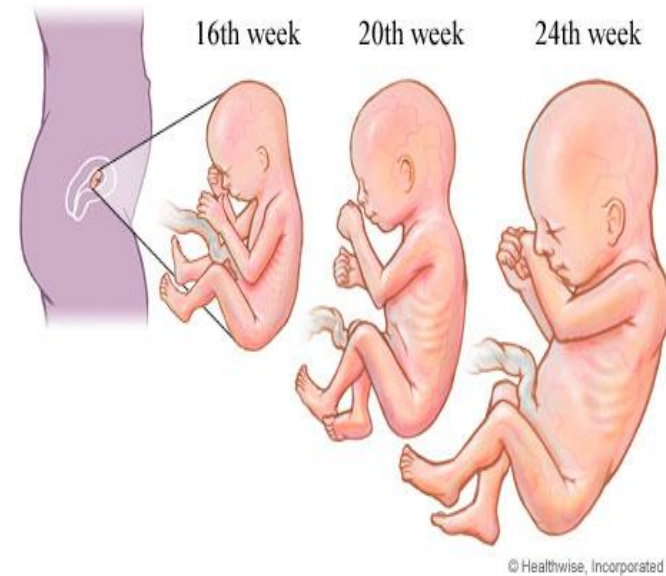


12th week



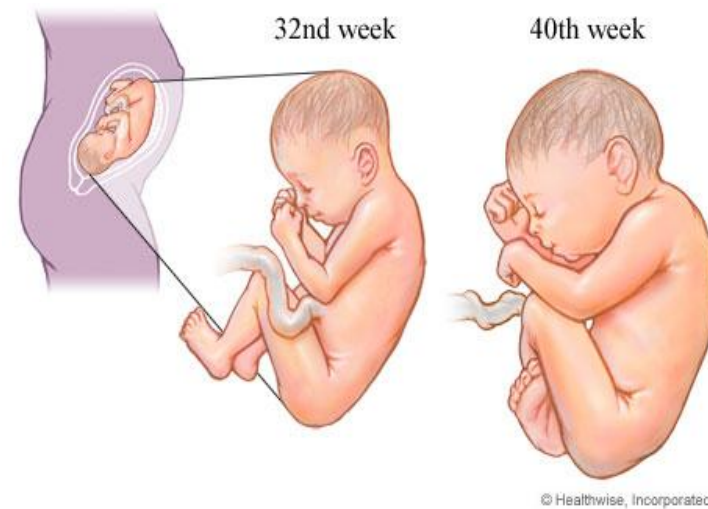
Second trimester of pregnancy

- During the **second trimester (4 to 6 months)** the baby is fully formed and just needs time to grow
- A women who is pregnant can mistakenly believe that her unborn baby is safe from anything consumed
- Health care provider should educate the mother that *exposure to certain substance can still harm the fetus (i.e. drug may have direct toxic effects)*



Last trimester of pregnancy

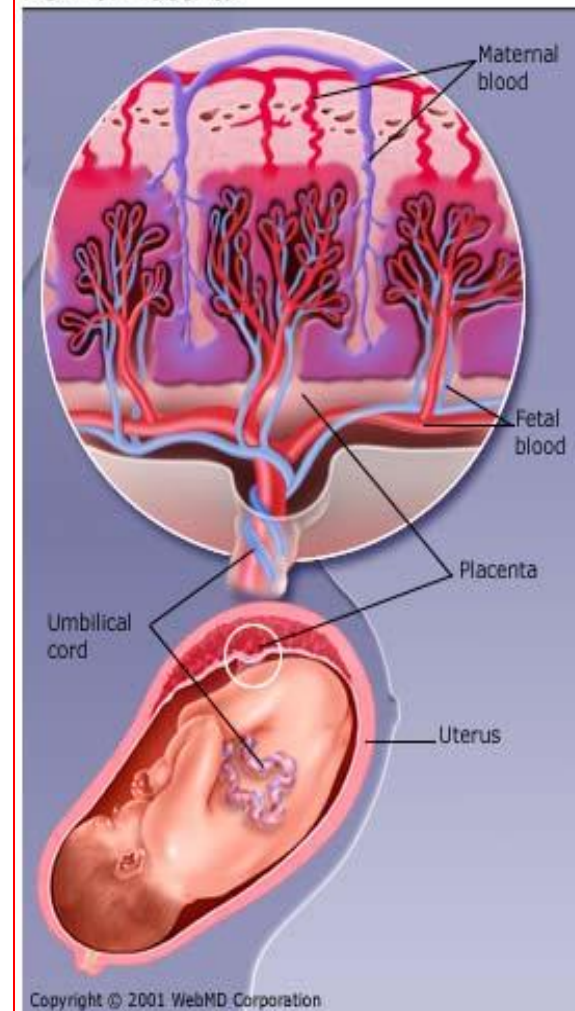
- During the last trimester (**7 to 9 months**):
 - ✓ Blood flow to the placenta increased
 - ✓ Placental vascular membrane become thinner
- Such alterations allow the transfer of more substance from the maternal circulation to the fetal blood
- As a result, **the fetus will receive larger doses of medications** and other substance taken by the mother



Placental transfer of drugs

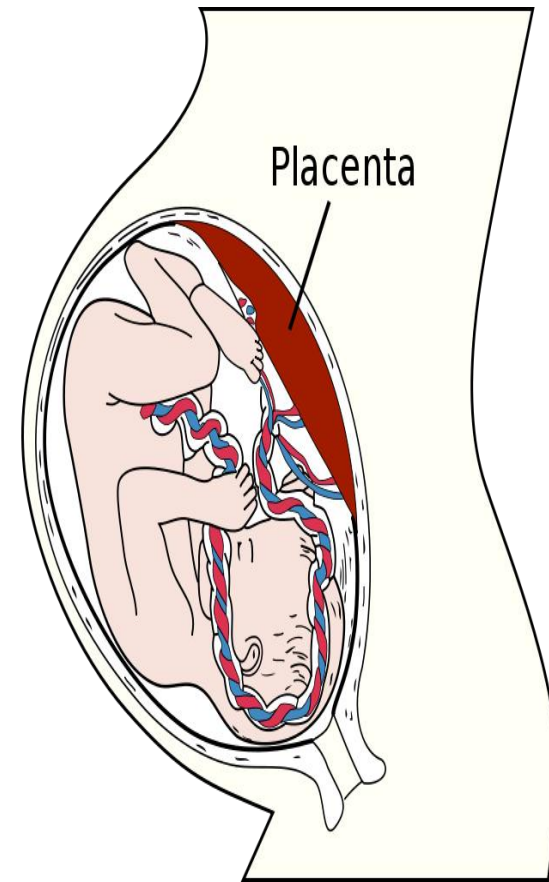
- **The placenta** is the **functional unit between the fetal and the maternal blood supply**
 - ✓ There is no mixing of the two system, but exchange of nutrients, oxygen, and waste products occurs primarily via **passive diffusion**
 - ✓ There is a few substance that are **actively transported** across the placenta
- For a drug to cause a teratogenic or pharmacological effect in the fetus, it must cross the maternal circulation to the fetal circulation
- Generally the principles that apply to drug transfer across any lipid membrane can be applied to placental transfer of drug

Normal Placenta



Factors that effect rate and extent of placental drug transfer

1. Molecular weight
2. Drug pKa
3. Lipid solubility
4. Drug absorption
5. Drug distribution
6. Plasma protein binding
7. Placental metabolism
8. Physical characteristics of the placenta
9. Maternal pharmacokinetics changes
10. Drug half life



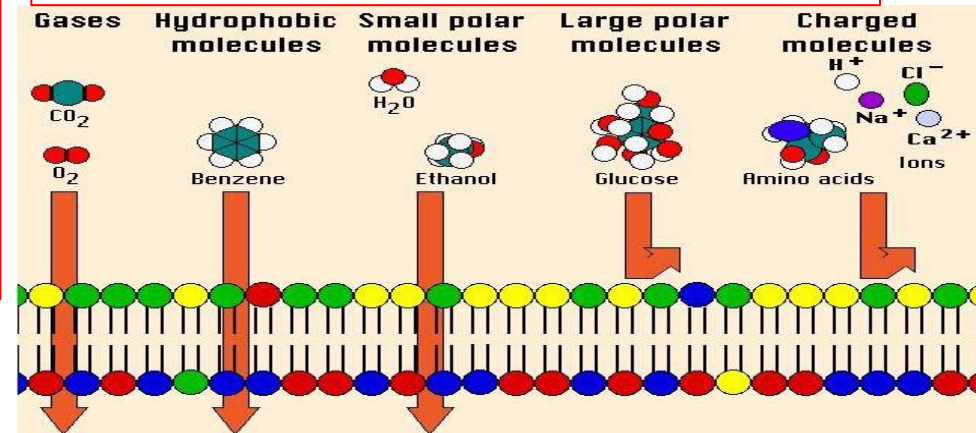
Factors that effect rate and extent of placental drug transfer

1- Molecular weight

- Low molecular weight drugs (500 Da) diffused freely across the placenta
- Drugs of higher molecular weight (500-1000 Da) cross less easily
- E.g. **Heparin** is very large molecule does not cross the placental membrane

2- Drug pKa

- Weakly **acidic** and weakly **basic** drugs tend to rapidly diffuse across the placental membranes
- **Ionized** compounds do not cross the placenta



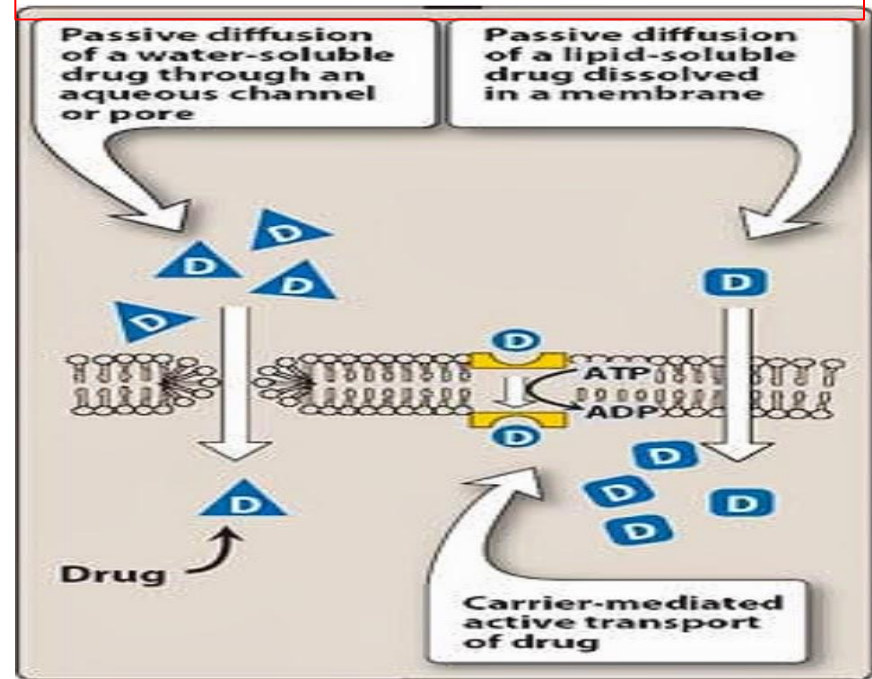
Factors that effect rate and extent of placental drug transfer

3- Lipid solubility

- Moderately **lipid soluble** drugs easily diffuse across the placental membrane
- It is important to note that **many drugs have been formulated for oral administration** and are designed for optimal lipid membrane transfer

4- Drug absorption

- **Nausea** and **vomiting** which are most common in the first trimester may effect absorption



Factors that effect rate and extent of placental drug transfer

5- Drug distribution

- The volume of distribution increases significantly during pregnancy and increases with advancing gestational age (i.e. $\uparrow$ plasma volume and $\uparrow$ total body fluid)
- **Hydrophilic drugs will have a higher volume of distribution**
 $\rightarrow \downarrow$ Plasma conc of the drugs
 $\rightarrow$ Less drugs is available to cross the placenta

6- Plasma protein binding

- **Highly plasma protein bound drug is less likely to cross the placenta, only free drug cross the placenta**
- **During pregnancy, a reduction in the levels of two major drug-binding protein is observed:**
 1. Albumin
 2. α_1 -acid glycoprotein
- ✓ This can increase the free fraction of drugs

Factors that effect rate and extent of placental drug transfer

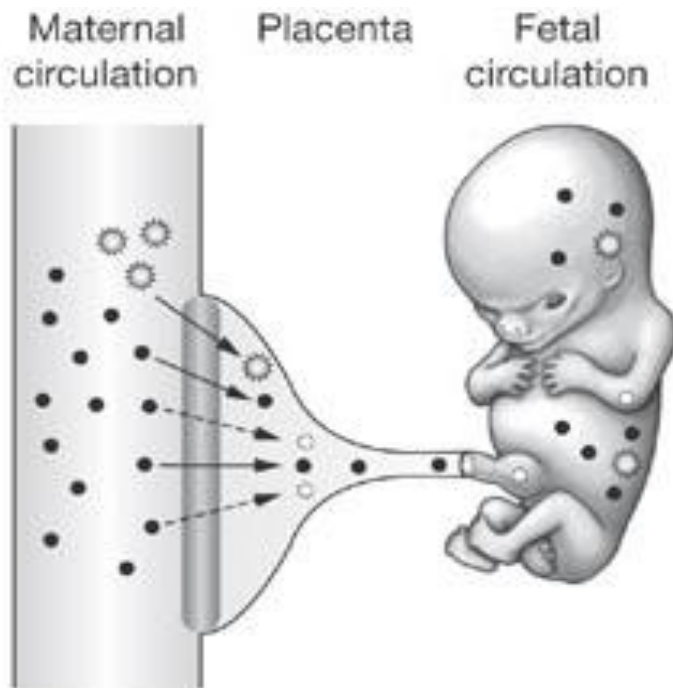
7- Placental metabolism

- Placenta produce enzymes that metabolised drugs

8- Physical characteristics of the placenta

- As a pregnancy progress, the placental membranes becomes progressively thinner

- ✓ Allow easier transfer of drugs a cross the placenta



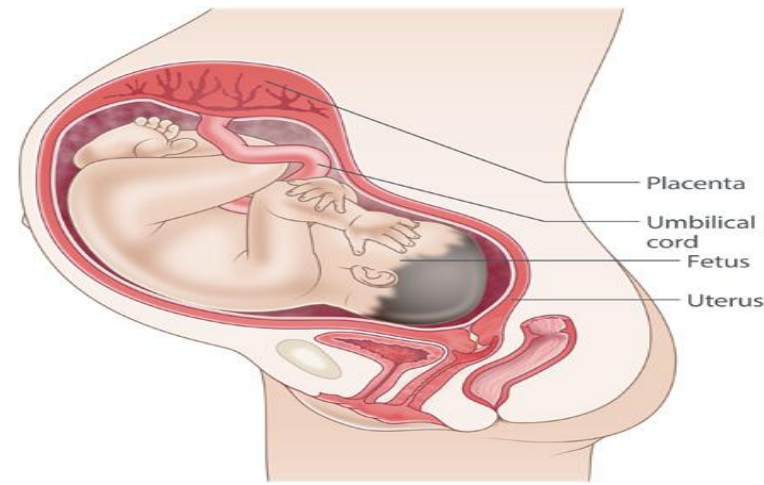
Factors that effect rate and extent of placental drug transfer

9- Maternal pharmacokinetics changes

1. **Dramatic increase in blood volume** occur during the first 30 weeks of pregnancy enhance blood flow to kidneys and liver (i.e. $\uparrow$ Clearance of drugs, $\downarrow$ exposure time to placenta)
 2. **Cytochrome p450 system enzymes changes:**
 - ✓ $\uparrow$ activity of 2D6, 2C9 and 3A4
 - ✓ $\downarrow$ or inhibition of 1A2 and 2C19
- Metabolism of some drugs is increase, whereas other decrease

10- Drug half-life

- Drugs that remain in circulation longer have a higher likelihood of placental passage due to prolonged exposure



Drug Therapy During Pregnancy

- The role of drugs in production of abnormalities in human is difficult to assess for two reasons:
 1. Most studies are **retrospective**, relying on the mother's memory for a history of exposure
 2. Pregnant women take **large number of drugs** (only 20% of pregnant women used no drugs during their pregnancy, according to National Institute of Health study)

Drug Therapy During Pregnancy

- In pre-existing conditions such as **diabetes**, **coagulation defect**, **epilepsy**, **hypertension** or **HIV infection** can risk the health of both the mother and the fetus if not treated so drugs are indicated
- we need to use **less harmful drugs**, **make dosage adjustment**, physician need to minimize their risk of toxicity to the mother and unborn baby
- Note: *fetus lacks mature metabolism, medications will have a prolonged duration of action within the unborn child*

Pregnancy Category	Description
A	<u>No risk to fetus</u> . Studies have not shown evidence of fatal harm
B	<u>No risk in animal studies</u> , and well controlled studies in pregnant women are not available. It is assumed there is little to no risk in pregnant women
C	<u>Animal studies indicate a risk to the fetus</u> , controlled studies on pregnant women not available. Risk versus benefit of the drug must be determined
D	<u>A risk to the human fetus</u> has been proved. Risk versus benefit of the drug must be determined . It could be used in life-threatening conditions
X	<u>A risk to the human fetus</u> has been proved. Risk outweighs the benefit , and <i>drug should be avoided during pregnancy</i>

Drug class	Teratogen (X)	Uncertain	Safe alternative
Antiemetics	-	-	Metoclopramide
Drugs for peptic ulcer	-	Omeprazole	Ranitidine
Laxative	-	-	•Lactulose •Docusate
Analgesics	-	Aspirin	Paracetamol
Antibiotics	-	Tetracycline	•Penicillin •Cephalosporin
Antihypertensives	ACE inhibitors	Diuretics	•Methyldopa •Clonidine
Antidiabetics	-	Oral hypoglycemic	Insulin
Anticoagulants	Warfarin	-	•Heparin •Low molecular weight heparin (LMWH)

Principles of prescribing during pregnancy

- Where possible **use nondrug therapy**
- Prescribe drugs only when **definitely needed**
- Choose the drug having the **best safety record** over time
- **Avoid newer drugs**, unless safety is clearly established
- **Over-the counter drugs can't be assumed to be safe**
- As far as possible, **avoid medication in the initial 10 weeks of gestation**
- Use the **lowest effective dose**
- Use drugs for the **shortest period** necessary
- If possible, give **drugs intermittently**

Drug of abuse during pregnancy

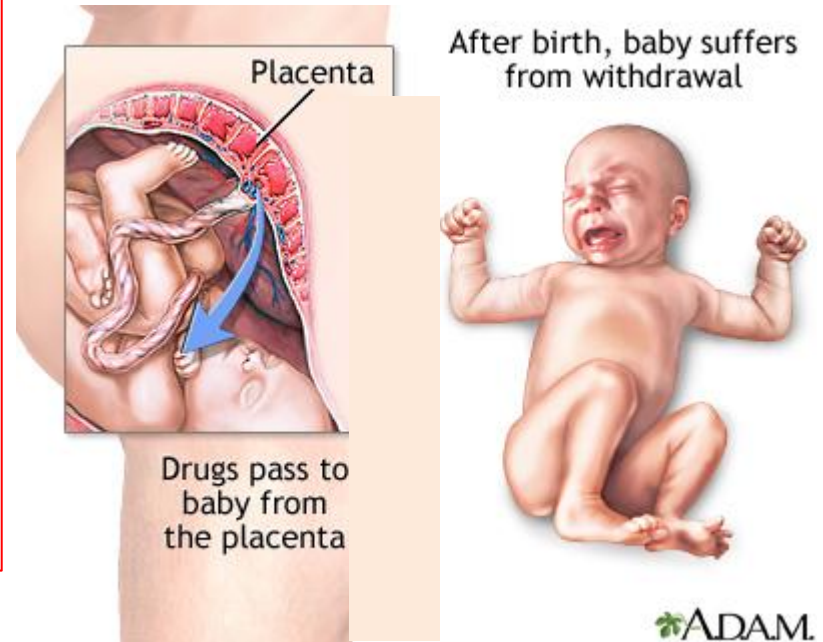
- One of the increase problems in today's society, especially in the western countries, is drugs of abuse during pregnancy such as:

- ✓ Cocaine
- ✓ Alcohol
- ✓ Nicotine (cigarette smoking)
- ✓ Marijuana
- ✓ Amphetamine
- ✓ Barbiturate
- ✓ Narcotics/ Opioids
- ✓ Benzodiazepine

Teratogen	Congenital Malformation
Cocaine	Growth retardation, microcephaly, behavioral abnormalities, gastroschisis
Alcohol	<u>Fetal alcohol syndrome</u> : short palpebral fissures, maxillary hypoplasia, heart defect, mental retardation
Marijuana	Fetal growth retardation
Nicotine	Miscarriage Low birth weight Delay in development
Amphetamine	Cleft lip palate, heart defect

Drug of abuse during pregnancy

- If the woman is abusing drugs during pregnancy her neonate may suffer from withdrawing syndrome



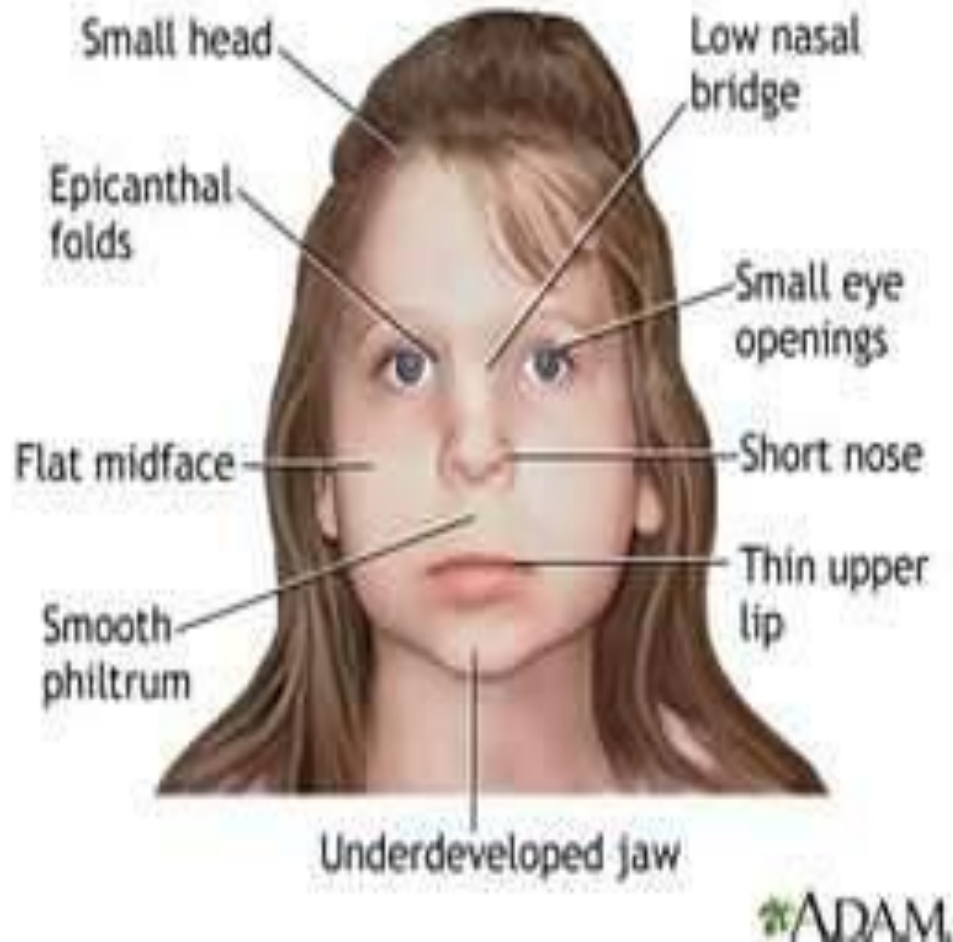
	Withdrawal Syndrome	
	General	CNS
Alcohol	Irritability Poor sleep pattern Diaphoresis	Crying, Hyperactivity, ↑Sensitivity to sound, Hypertonicity, Tremors, Seizure
Cocaine	Poor sleep pattern Tremulousness	Hypotonia, hyperreflexia
Marijuana	-	Tremor, ↑Sensitivity to sound
Nicotine	Mild ↑muscle tone	Tremor
Phenobarbital	Irritability, poor sleep pattern, diaphoresis, skin abrasions	Excessive crying, hyperreflexia, Hypertonicity, Tremors, Seizure
Diazepam	Hypothermia	Hyperactivity, Hypertonicity, Tremors, Seizure
Opioids: Morphine Heroin	Irritability, wakefulness, Yawning, fever, diaphoresis, poor sleep pattern, hypothermia	Tremor, seizure, Hyperreflexia, Hyperactivity, ↑Sensitivity to sound, Hypertonicity, photophobia

Fetal alcohol syndrome (FAS)

- There is a well-documented association between maternal alcohol ingestion with:
 - ✓ Growth restriction
 - ✓ Craniofacial dysmorphology
 - ✓ CNS malfunctions
 - ✓ Various other abnormalities
- Even moderate alcohol consumption during pregnancy may be detrimental to embryonic development
- The CNS is particularly sensitive to alcohol and alcohol-related neurodevelopmental disorder (ARND) may result from exposure

- The incidence of FAS and ARND together is 1 in 100 live births
- Furthermore, Alcohol increase rate of spontaneous abortion

Fetal alcohol syndrome (FAS)



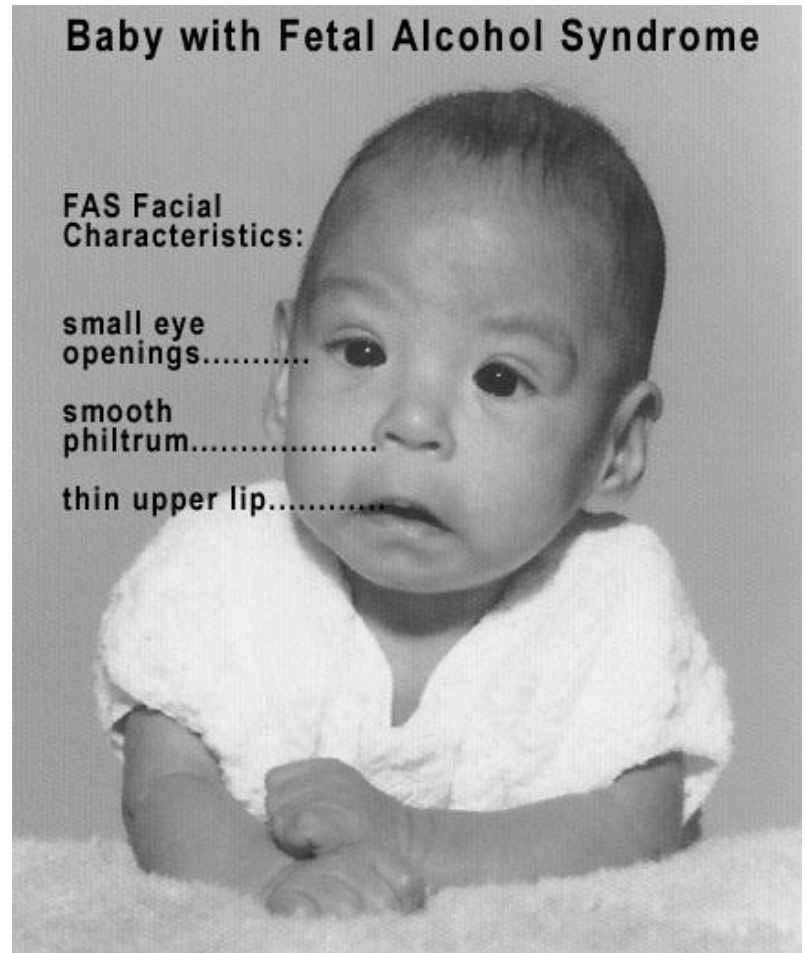
Baby with Fetal Alcohol Syndrome

FAS Facial Characteristics:

small eye openings.....

smooth philtrum.....

thin upper lip.....



Cigarette smoking during pregnancy

- **Cigarette** contain many toxic and carcinogenic compounds in addition to nicotine
- **Nicotine** is a potent **VC** capable of:
 - ✓ Reducing uterine blood flow
 - ✓ Increaseing uterine vascular resistance
- Smoking during pregnancy increase risk of:
 1. Growth restrictions
 2. Spontaneous abortion
 3. Premature delivery
 4. Placental abruption and premature rupture of the membrane
 5. Small increase in defect of the heart, limbs, feet, skull...etc

